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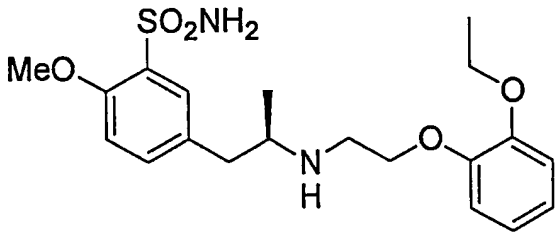
(54) Title: A METHOD OF THE PREPARATION OF (R)-(-)-5'2-'2-(2-ETHOXYPHENOXY)ETHYLAMINO! PROPYL!-2-METHOXYBENZENESULPHONAMIDE (TAMSULOSIN)

(57) Abstract: The compound of formula (I) is obtained via reaction of a compound of formula (III), or (VII), with a compound of formula (IV).

A METHOD OF THE PREPARATION OF (R)-(-)-5'2-'2-(2-ETHOXYPHENOXY)ETHYLAMINO! PROPYL!-2-METHOXYBENZENESULPHONAMIDE (TAMSULOSIN)

Technical Field

The invention relates to a method of preparing (R)-(-)-5-[2-[2-(2-ethoxyphenoxy)ethylamino]propyl]-2--methoxybenzenesulphonamide (termed tamsulosine below) of formula I

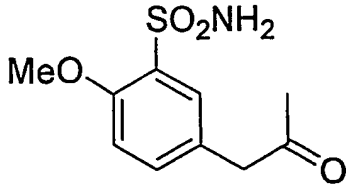


(I)

Background Art

The compound I has been known as a selective blocker of α_{1C} receptors, which allows its use for a treatment of urine-retention problems in connection with hyperplasic prostate without influencing blood pressure. This property distinguishes the compound I from a number of other blockers of α_1 receptors, which do not act selectively and, therefore, show side effects in the form of hypotension connected with various unpleasant conditions for the patient (e.g. EP 710 486).

A mixture of (R) and (S) enantiomers of 5-[2-[2-(2-ethoxyphenoxy)ethylamino]propyl]-2--methoxybenzenesulphonamide (termed racemic tamsulosine below) was described in the patent EP 34 432. The method of preparation of the group of derivatives of sulphamoyl-phenylethylamine consisted in reductive amination (or amination and subsequent reduction)



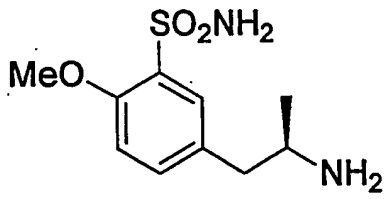
of ketones of the type II.

(II)

The group of compounds described in the patent EP 34 432 was characteristic for their ability to block α adrenergic receptors, which led to their use in treating a number of illnesses, especially hypertension, congestive heart failure or problems related to the urinary tract.

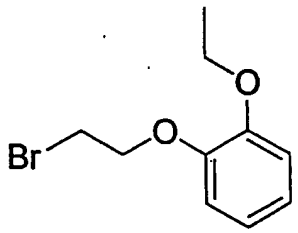
It turned out later that the above-mentioned compound I, specifically its (R)-enantiomer, shows a selective effect during treatment of problems related to hyperplasic prostate without influencing blood pressure or heart action. (Honda K. and Nakagawa C: Alpha –1-adrenoreceptor antagonist effect of optical isomers YM-12617 in rabbit lower urinary tract and prostate- J. Pharm Exp. Ther. 239, 512, (1986)).
This led to the effort to effectively synthesize the optically active compound I.

The Austrian patent AT 397960 presented a synthesis of (R)-tamsulosine (I) using the reaction of an optically active amine III



(III)

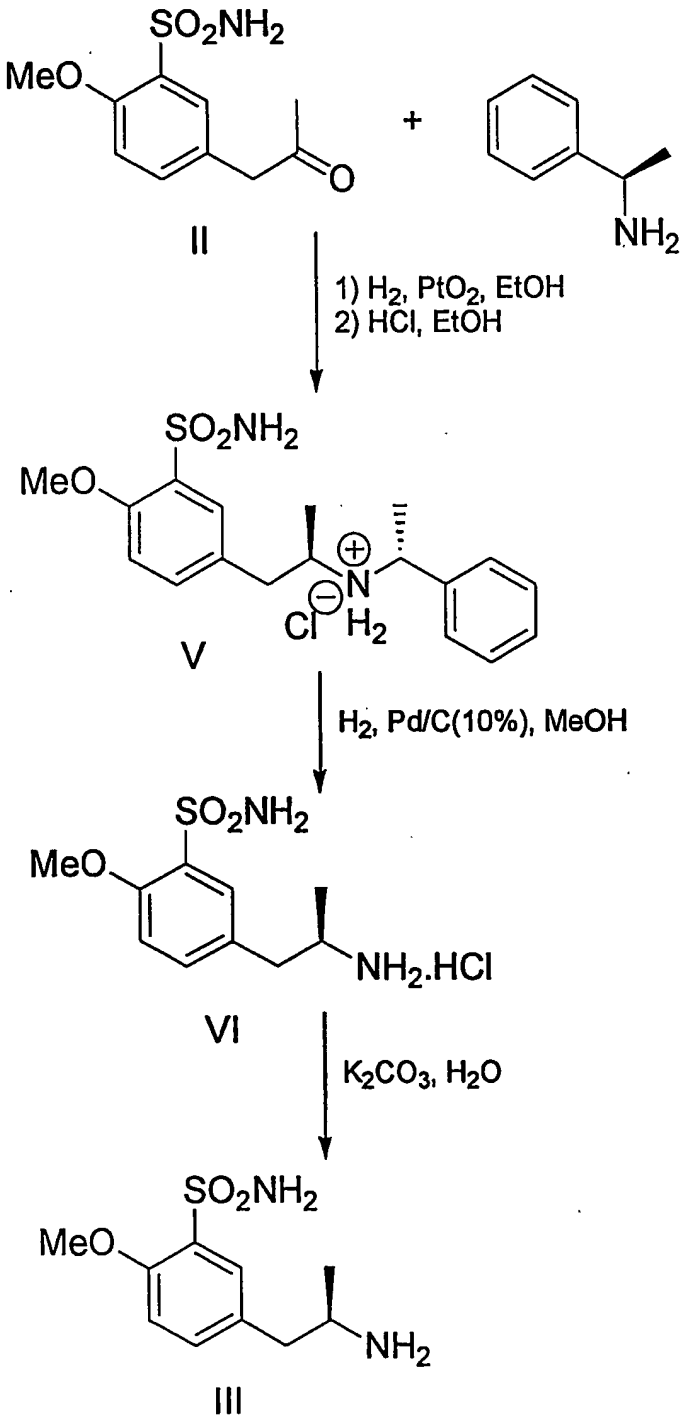
with a brominated ether of formula IV



(IV)

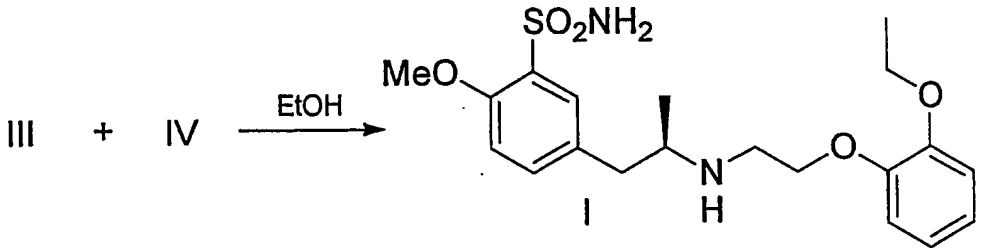
The synthesis turned out to be very advantageous if the entering amine III was prepared using the procedure described in patent EP 257785, or alternatively in the divisional EP 380144.

The patents describe the path outlined in the following scheme:



The reaction of ketone II with (R)-α–methylbenzylamine in an reductive environment under Pt-catalysis results in the optically active (R,R)-diastereoisomer V having a high optical purity (about 92 %). This intermediate is subsequently re-crystallized to achieve high optical purity and it is transformed to optically active (R)-hydrochloride VI using hydrogenolysis. (R)-hydrochloride VI is transformed to (R)-amine of the formula III using a base.

A certain shortcoming of the procedure is its last stage



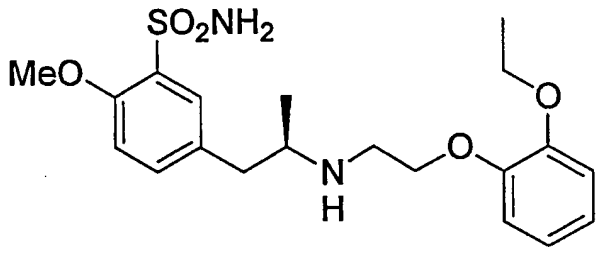
(R)-amine III is alkylated with bromide IV in such a way that an excess of the expensive amine is used (2 equivalents) and the reaction is performed via prolonged boiling in ethanol (16 hours). The reaction mixture is subjected to alkaline processing and the crude product, which contains unreacted starting amine III, is purified using column chromatography. The obtained base of tamsulosine I is finally converted to its hydrochloride.

In addition to the outlined main reaction of compounds III and IV, this setting also gives rise to reaction of the resulting hydrogen bromide with optically active amine III, which shifts the equilibrium towards product I.
However, considering production costs, it is quite inefficient to use expensive amine III to bind hydrogen bromide. Another disadvantage is the chosen solvent (ethanol) since the reaction rate is slow in this medium and prolonged heat exposure results in formation of impurities. After the reaction is complete, it is then necessary to purify the product using a very demanding and sub-optimal method, from the process point of view, - the column chromatography.

However, it has turned out now that the reaction can be performed in an equimolar ratio of the compounds III and IV.

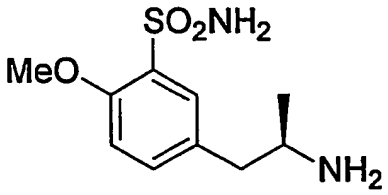
The essence of the invention

The invention relates to the preparation of (R)-(-)-5-[2-[2-(2-ethoxyphenoxy)ethylamino]propyl]-2-methoxybenzenesulphonamide, i.e. of the compound of the formula I,

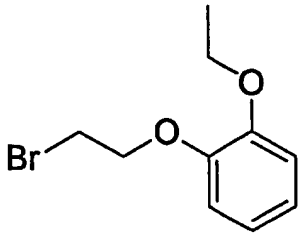


I

via reaction of the compound of formula III with the compound of formula IV



III



IV

consisting in using the compounds III and IV in the molar ratio $X_M = N_{IV}/N_{III}$, equal to from 1 to 1.1,

wherein N_{III} and N_{IV}, resp., are numbers of mols of the compounds III and IV, respectively, entering the reaction. The reaction is carried out in the presence of an inexpensive base and in the environment of a polar aprotic solvent.

When using reaction components in the molar ratio close to 1:1 it is necessary to prevent the subsequent reaction of hydrogen bromide with optically active amine III and, at the same time, ensure a shift of the reaction equilibrium towards the product I.

It has turned out that it is possible to perform simultaneously with the main reaction of the compounds III and IV a type of reaction that would compete with the undesirable conversion of amine III to useless hydrobromide whereas, the byproduct of the main reaction, hydrogen bromide, can be channeled away via this competing reaction, possibly irreversibly. This, in turn, effectively prevents creation of the hydrobromide. The reaction rate of the contemplated competing reaction depends first of all on the choice of the external reagent. For this purpose, it is an advantageous to opt for such a base that is dissociated more than amine III in the given reaction environment.

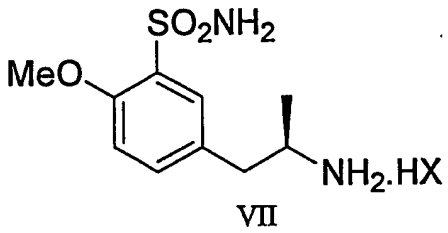
In practice, it is possible to use a varied selection of inexpensive bases such as carbonates or hydrogencarbonates of alkali metals, or organic tertiary bases like, for example, diisopropyl(ethyl)amine.

The choice of solvent is also crucial for the reaction of the invention, which solvent forms, to a substantial extent, the reaction environment, which will influence velocity of the main reaction of amine III with brominated ether IV. In the same way, it impacts other reactions that lead to undesirable products. It turns out that some suitable examples of such solvents are dialkylamides, e.g. dimethylformamide, dimethylacetamide, N-methylpyrrolidone, or dialkylsulphoxides, such as, for example, dimethylsulphoxide, sulpholane.

The third important factor is temperature, which can range from 60 to 140 ^{0}C.

In our view, an especially advantageous setting is the one in which the reaction runs in dimethylformamide or dimethylsulphoxide in the presence of potassium carbonate at temperatures 60 up to 140 ^{0}C for 2 to 8 hours.

This new way of synthesizing tamsulosine (I) also allows for combining two reaction steps and using, in the alkylation reaction, directly the salts of (R)-amine of formula VII



VII

wherein HX stands for an inorganic or organic acid such as, for example, hydrochloric acid (HX = HCl), hydrobromic acid (HX = HBr), acetic acid (HX = CH_3COOH) or propionic acid (HX = CH_3CH_2COOH),
along with bromide IV under the above-stated conditions since the present inexpensive base releases amine III directly in the reaction mixture, and this is subsequently alkylated with bromide IV (a one-pot design).

Moreover, beside the increased yield, production work expenditure decreases as well.

The following examples are illustrative, but by no means limiting, of the universal character of the embodiment according to the invention.

Example 1

Anhydrous sodium carbonate (83.2 g; 0.78 mol) is added to the solution of (R)-(-)-5-(2-aminopropyl)-2-methoxybenzenesulphonamide (208 g; 0.85 mol) and 2-(2-ethoxyphenoxy)ethylbromide (220 g; 0.90 mol) in N,N-dimethylformamide (1.3 L) and the reaction mixture is stirred and heated for 5 hours under a reflux condenser at a temperature of 60 – 70°C. After cooling down, water is added (1.5 L) and the mixture is extracted with ethyl acetate (3 x 1 L). Combined organic phases are washed with water (2x1 L). The solvent is evaporated and ethanol (0.3 L) is added to the evaporation residue; the crystals are sucked off and washed with ethanol. Dry crystals of tamsulosine base (197 g; 57% of the theoretical yield) are stirred up in ethanol (3.5 L) and acidified with ethanolic hydrogen chloride (0.5 L). The suspension is stirred for 2 hours at lab temperature. The crystals are sucked off and washed with ethanol. The obtained tamsulosine hydrochloride (194 g; 51% of the theoretical yield) is purified by releasing the base with 10% aqueous solution of sodium hydroxide in ethanol and repeated conversion to tamsulosine hydrochloride with ethanolic hydrogen chloride in ethanol.

The yield was 180 g (47.5% of the theoretical yield).

Melting point 228 – 230°C, $[\alpha]_D$= -3.63°(c=1.02; methanol)

Example 2

Anhydrous sodium carbonate (0.5 g; 4.7 mmol) is added to the solution of (R)-(-)-5-(2-aminopropyl)-2-methoxybenzenesulphonamide (1.25 g; 5.1 mmol) and 2-(2-ethoxyphenoxy)ethylbromide (1.25g; 5.1 mmol) in dimethylsulphoxide (20 ml) and the reaction mixture is stirred and heated for 2 hours under a reflux condenser at a temperature of 90 - 95°C. After cooling down, water is added (20 ml) and the mixture is extracted with ethyl acetate (3 x 20 ml). Combined organic phases are washed with water (3x20 ml). The solvent is evaporated and ethanol (65 ml) is added to the evaporation residue. The mixture is acidified with ethanolic hydrogen chloride (12 ml). The suspension is stirred for 2 hours at lab temperature. The crystals are sucked off and washed with ethanol.

The yield was 1.12 g (54.1% of the theoretical yield).

Melting point 228.5 – 230°C, $[\alpha]_D$= -3.6°(c=1.00;methanol)

Example 3

Anhydrous sodium carbonate (139.3 g; 1.31 mol) is added to the solution of (R)-(-)-5-(2-aminopropyl)-2-methoxybenzenesulphonamide, acetate (212 g; 0.7 mol) and 2-(2-ethoxyphenoxy)ethylbromide (208.8 g; 0.85 mol) in N,N-dimethylformamide (1.3 L) and the reaction mixture is stirred and heated for 9 hours under a reflux condenser at a temperature of 60 – 70°C. After cooling down, water is added (1.3 L) and the mixture is extracted with ethyl acetate (3 x 0.85 L). Combined organic phases are washed with water (3x500 ml). The solvent is evaporated and ethanol (0.2 L) is added to the evaporation residue; the crystals are sucked off and washed with ethanol. Dry crystals of tamsulosine base (154 g; 54% of the theoretical yield) are stirred up in ethanol (2.8 L) and acidified with ethanolic hydrogen chloride (0.38 L). The suspension is stirred for 2 hours at lab temperature. The crystals are sucked off and washed with ethanol. The obtained tamsulosine hydrochloride (153 g; 49.4% of the theoretical yield) was purified by releasing the base with 10% aqueous solution of sodium hydroxide in ethanol and repeated conversion to tamsulosine hydrochloride with ethanolic hydrogen chloride in ethanol.

The yield was 142 g (45.8% of the theoretical yield).

Melting point 227.5 – 229.5°C, $[\alpha]_D$= -3.6°(c=1.01;methanol)

Example 4

Anhydrous sodium carbonate (1.3 g; 12 mmol) is added to the solution of (R)-(-)-5-(2-aminopropyl)-2-methoxybenzenesulphonamide, hydrochloride (1.45 g; 5.1 mmol) and 2-(2-ethoxyphenoxy)ethylbromide (1.36 g; 5.5 mmol) in N,N-dimethylformamide (20 ml) and the reaction mixture is stirred and heated for 8 hours under a reflux condenser at a temperature of 95 – 105°C. After cooling down, water is added (20 ml) and the mixture is extracted with ethyl acetate (3 x 20 ml). The solvent is evaporated and ethanol (10 ml) is added to the evaporation residue. The crystals are sucked off and washed with ethanol. Dry crystals of tamsulosine base (1.1 g; 54.3% of the theoretical yield) are stirred up in ethanol (20 ml) and acidified with ethanolic hydrogen chloride (7 ml). The suspension is stirred for 2 hours at lab temperature. The crystals are sucked off and washed with ethanol. The obtained tamsulosine hydrochloride (1.0 g; 45 % of the theoretical yield) was purified by releasing the base with 10% aqueous solution of sodium hydroxide in ethanol and repeated conversion to tamsulosine hydrochloride with ethanolic hydrogen chloride in ethanol.
The yield was 0.89 g (40% of the theoretical yield).
Melting point 227.5 – 230°C, $[\alpha]_D$= -3.4°(c=0.99;methanol)

Example 5

Anhydrous sodium carbonate (0.5 g; 4.7 mmol) is added to the solution of (R)-(-)-5-(2-aminopropyl)-2-methoxybenzenesulphonamide (1.25 g; 5.1 mmol) and 2-(2-ethoxyphenoxy)ethylbromide (1.25 g; 5.1 mmol) in N-methylpyrrolidone (20 ml) and the reaction mixture is stirred and heated for 6 hours under a reflux condenser at a temperature of 65 - 75°C. After cooling down, water is added (30 ml) and the mixture is extracted with ethyl acetate (3 x 30 ml). Combined organic phases are washed with water (2x20 ml). The solvent is evaporated and ethanol (15 ml) is added to the evaporation residue. The mixture is acidified with ethanolic hydrogen chloride (5 ml). The formed suspension is stirred for 2 hours at lab temperature; the crystals are sucked off and washed with ethanol.
The yield was 1.11 g (49.1% of the theoretical yield).
Melting point 228 – 230.5°C, $[\alpha]_D$= -3.6°(c=1.01;methanol)

Example 6

Anhydrous diisopropylethylamine (Huenig's base; 1.85 ml; 10.8 mmol) is added to the solution of (R)-(-)-5-(2-aminopropyl)-2-methoxybenzenesulphonamide (2.45 g; 10 mmol) and 2-(2-ethoxyphenoxy)ethylbromide (2.5g; 10.2 mmol) in dimethylsulphoxide (40 ml) and the reaction mixture is stirred and heated for 4 hours under a reflux condenser at a temperature of 90 - 95°C. After cooling down, water is added (50 ml) and the mixture is extracted with ethyl acetate (3 x 50 ml). Combined organic phases are washed with water (3x40 ml). The solvent is evaporated and ethanol (55 ml) is added to the evaporation residue. The mixture is acidified with ethanolic hydrogen chloride (15 ml). The formed suspension is stirred for 2 hours at lab temperature. The crystals are sucked off and washed with ethanol. The yield was 2.15 g (48.3% of the theoretical yield).
Melting point 228.5 – 230.5°C, $[\alpha]_D$= -3.5°(c=0.98;methanol)

Example 7

Anhydrous potassium hydrogen-carbonate (0.97 g; 9.7 mmol) is added to the solution of (R)-(-)-5-(2-aminopropyl)-2-methoxybenzennsulphonamide (1.10 g; 4.5 mmol) and 2-(2-ethoxyphenoxy)ethylbromide (1.21g; 4.95 mmol) in dimethylacetamide (20 ml) and the reaction mixture is stirred and heated for 4 hours under a reflux condenser at a temperature of 135 - 145°C. After cooling down, water is added (30 ml) and the mixture is extracted with ethyl acetate (3 x 40 ml). Combined organic phases are washed with water (2x20 ml). The solvent is evaporated and ethanol (25 ml) is added to the evaporation residue. The mixture is acidified with ethanolic hydrogen chloride (5 ml). The formed suspension is stirred for 2 hours at lab temperature. The crystals are sucked off and washed with ethanol.
The yield was 0.8 g (40.1% of the theoretical yield).
Melting point 227 – 229.5°C, $[\alpha]_D$= -3.5°(c=1.1;methanol)

Example 8

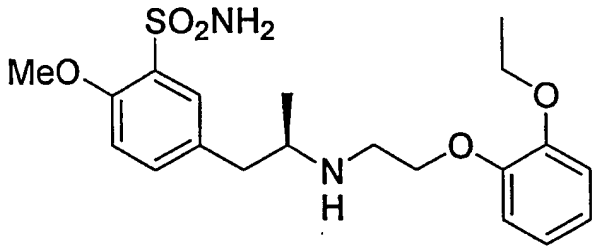
Anhydrous sodium hydrogen-carbonate (1.01 g; 12 mmol) is added to the mixture of propionate of (R)-(-)-5-(2-aminopropyl)-2-methoxybenzenesulphonamide (1.91 g; 6.0 mmol), 2-(2-ethoxyphenoxy)ethylbromide (1.62g; 6.6 mmol) and sulpholane (30 g) and the reaction mixture is stirred and heated for 12 hours under a reflux condenser at a temperature of 90 - 95°C. After cooling down, water is added (50 ml) and the mixture is extracted with ethyl acetate (3 x 50 ml). Combined organic phases are washed with water (3x25 ml). The solvent is evaporated and ethanol (65 ml) is added to the evaporation residue.

The mixture is acidified with ethanolic hydrogen chloride (17 ml). The formed suspension is stirred for 2.5 hours at lab temperature. The crystals are sucked off and washed with ethanol. The yield was 0.92 g (34.4% of the theoretical yield).

Melting point 228 – 230°C, $[\alpha]_D$= -3.5°(c=1.05;methanol)

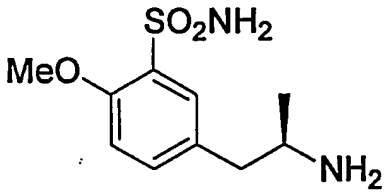
CLAIMS

1. A method of the preparation of (R)-(-)-5-[2-[2-(2-ethoxyphenoxy)ethylamino]propyl]-2--methoxybenzenesulphonamide of formula I

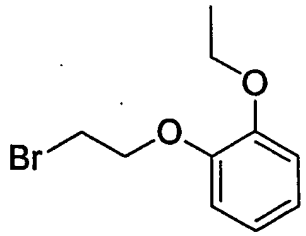


I

via the reaction of the compound of formula III or its acid addition salt with a compound of the formula IV,



III



IV

characterized in that the compounds of formulae III and IV are used in a molar ratio $X_M = N_{IV}/N_{III}$ equal to from 1 to 1.1; wherein N_{III} and N_{IV} stand for number of mols of the compounds III and IV, respectively, entering the reaction.

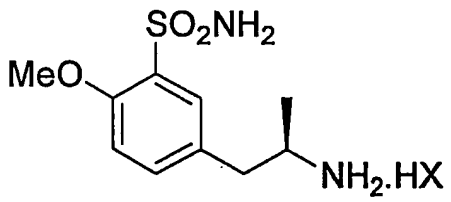
2. The method in accordance with claim 1, *characterized in* that the reaction is performed in the presence of an external base.

3. The method in accordance with claim 2, *characterized in* that the external base is selected from among carbonates or hydrogen-carbonates of alkali metals or organic tertiary amines.

4. The method in accordance with claim 1 or 2, *characterized in* that the reaction is performed in a polar aprotic solvent.

5. The method in accordance with claim 4, *characterized in* that the mentioned solvent is selected from among dialkylamides, such as dimethylformamide, dimethylacetamide, or N-methylpyrrolidone, or dialkylsulphoxides, such as dimethylsulphoxide or sulpholane.

6. The method in accordance with any of the preceding claims, *characterized in* that a salt of amine of formula VII



VII

wherein HX stands for an inorganic or organic acid that is gradually converted to a reacting base III during the course of the reaction,
enters the reaction simultaneously with the compound of formula IV.

7. The method in accordance with claim 6, *characterized in* that the inorganic or organic acid is hydrochloric acid or hydrobromic acid, or acetic acid or propionic acid.

8. The method in accordance with claims 1 or 6, *characterized in* that the reaction takes place in dimethylformamide or dimethylsulphoxide in the presence of an alkali carbonate, preferably of potassium or sodium carbonate, at a temperature of from 60 to 140 ^{0}C for 2 to 8 hours.

9. The method in accordance with any of the preceding claims, *characterized in* that the molar ratio of the compounds III and IV X_M is equal to from 1.02 to 1.05.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CZ 02/00053

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C303/40 C07C311/37

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AT 397 960 B (YAMANOUCHI PHARMACEUTICAL CO LTD) 25 August 1994 (1994-08-25) cited in the application page 5, line 47-49 ---	1-9
A	EP 0 710 486 A (YAMANOUCHI PHARMA CO LTD ;YAMANOUCHI UK LTD (GB)) 8 May 1996 (1996-05-08) cited in the application the whole document -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
30 January 2003	05/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Goetz, G

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/CZ 02/00053

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